Rationale for co-targeting IGF-1R and ALK in ALK fusion-positive lung cancer.

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Public Summary:
Crizotinib, a selective tyrosine kinase inhibitor (TKI), shows marked activity in patients whose lung cancers harbor fusions in the gene encoding anaplastic lymphoma receptor tyrosine kinase (ALK), but its efficacy is limited by variable primary responses and acquired resistance. In work arising from the clinical observation of a patient with ALK fusion-positive lung cancer who had an exceptional response to an insulin-like growth factor 1 receptor (IGF-1R)-specific antibody, we define a therapeutic synergism between ALK and IGF-1R inhibitors. Similar to IGF-1R, ALK fusion proteins bind to the adaptor insulin receptor substrate 1 (IRS-1), and IRS-1 knockdown enhances the antitumor effects of ALK inhibitors. In models of ALK TKI resistance, the IGF-1R pathway is activated, and combined ALK and IGF-1R inhibition improves therapeutic efficacy. Consistent with this finding, the levels of IGF-1R and IRS-1 are increased in biopsy samples from patients progressing on crizotinib monotherapy. Collectively these data support a role for the IGF-1R-IRS-1 pathway in both ALK TKI-sensitive and ALK TKI-resistant states and provide a biological rationale for further clinical development of dual ALK and IGF-1R inhibitors.

Scientific Abstract:
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